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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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GOLDBERG, J

ART UNIT	PAPER NUMBER
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022829
ROCHE MOLECULAR SYSTEMS INC
PATENT LAW DEPARTMENT
1145 ATLANTIC AVENUE
ALAMEDA CA 94501

HM22/0725

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

1- File Copy

Office Action Summary	Application No. 09/465,491	Applicant(s) CHANG ET AL.	
	Examiner Jeanine A Enewold Goldberg	Art Unit 1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 June 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-8,10,12-21,23 and 25-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5-8,10,12-21,23 and 25-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed June 18, 2001. Currently, claims 1, 3, 5-8, 10, 12-21, 23, 25-27 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

2. Any objections and rejections not reiterated below are hereby withdrawn.

3. This action is FINAL.

Maintained Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 8-14, 21-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

B) Claims 21-27 are indefinite because the method does not provide how to identify cancerous cells by using the hTERT mRNA quantitation. The method appears to be missing steps with regard to how the hTERT is related to the cancerous cells. The method does not provide how to identify if cancerous cells are present based upon the quantity of mRNA. Claims 21-27 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are directed to how the hTERT mRNA is used to identify cancerous cells.

Response to Arguments

The response traverses the rejection. The response asserts that "it is not a function of the claims to specify how each step is carried out. This is a function of the specification". This argument has been reviewed but is not convincing because the claim does not provide the means for identifying the presence of cancer cells in a sample. The examiner notes that the specification is read in light of the claims, however limitations from the specification are not read into the claims. The claims only provide quantitating hTERT mRNA and identifying if cancerous cells are present. The claim provides no guidance as to how to identify if cancerous cells are present. The response points to Example 7, however, Example 7 discusses a threshold to value. The specification does not provide the threshold value. Thus, the specification does not clearly outline the steps necessary to determine whether cancerous cells are present. Thus for the reasons above and those already of record, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1, 3, 5-7, 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kilian et al (Human Molecular Genetics, Vol. 6, No. 12, pg. 2011-

2019, 1997) in view of Hudkins et al. (US Pat. 5,475,110, December 1995) further in view of Nakamura et al (Genbank Accession Number AF015950, August 1997).

Kilian et al. (herein referred to as Kilian) teaches the beta deletion in the hTCS1 gene (also referred to as hTERT, see specification pg. 1). Kilian teaches that the beta-exon deletion encode truncated proteins. Kilian teaches regions surrounding the beta-exon deletion region (see Figure 5). Kilian teaches numerous oligonucleotide primers which include HT2356R. HT2356R is located within exon 8 and overlaps the last 7 nucleotides of SEQ ID NO: 4. Kilian teaches that hTCS1 is differentially expressed in normal and tumor tissues. As seen in Figure 4, TR-PCR was carried out on RNA with primer combinations including HT2356R (limitations of Claim 3). Kilian teaches southern and Northern analysis using P-labeled probes, RT-PCR analysis using electrophoresis in a agarose gel and probing with a radiolabeled oligonucleotide (pg 2017, col. 2). Finally, Kilian teaches that the beta-exon deletion encodes a truncated protein.

While Kilian teaches probing with radiolabeled probes and studying of expression levels, it is not apparent that Kilian explicitly teaches quantifying the PCR product obtained.

Hudkins et al. (herein referred to as Hudkins) teaches analysis and quantification of mRNA after separation on agarose gels. Hudkins teaches the RNA was transferred and the blots were hybridized with P-labeled probes, washed and placed in a phosphorimagining cassettes such that the density (i.e. amount of RNA) is expressed as relative pohsphorimager units (col. 19, lines 34-55).

While Kilian teaches a primer which is located in exon 8 and overlaps the last 7 nucleotides of SEQ ID NO: 4, neither Hudkins nor Kilian specifically teach the primers and probes of the instant case.

Nakamura however teaches the entire sequence of the hTERT gene.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the primers of Kilan for detection of hTERT mRNA since the entire hTERT sequence was taught and characterized by Nakamura. Additionally, in the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologues, *however*, the court stated

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologues because homologues often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed primers simply represent structural and functional homologues of the full length disclosed hTERT sequence concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited reference in the absence of secondary considerations. Designing primers and probes which are equivalents to those taught in the art is routine experimentation. The ordinary artisan would have been motivated to have designed probes and primers based upon the sequence of Nakurma

which were functional equivalents to those provided by Kilian. Absent factual evidence that the instant primers have unexpected benefits or properties such that they would not be equivalents to those provided in the art, the claimed primers are merely functional equivalents of the primers provided in the art for amplifying the hTERT gene.

Moreover, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kilian which detects mRNA of hTCS1 with the method of Hudkins for quantifying RNA. The skilled artisan would have been motivated to have quantitated the mRNA obtained in the method of Kilian for the expected benefit of quantifying the amount of mRNA present. Quantification of mRNA, at the time the invention was made, was a well known method which provided information regarding transcriptional activity of the mRNA and may be used to study the expression of one gene relative to another gene. Thus, the ordinary artisan would have numerous reasons for desiring a quantitative value for the mRNA of hTERT.

Response to Arguments

The response traverses the rejection. The response asserts that the claimed primers are not obvious. The response assert that the particular primers are critical aspect of all of the claims since the particular primers enable a significantly improved quantiation of hTERT mRNA.

The response asserts that the particular primers are not structural and functional homologues of the full length hTERT sequence. This argument has been reviewed but is not convincing because as stated in the rejection above, it would have been prima

facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the primers of Kilan for detection of hTERT mRNA since the entire hTERT sequence was taught and characterized by Nakamura. Given the primers taught in the art, namely HT2026F and HT2356R of Kilian, the ordinary artisan would have been motivated to have modified the primers of Kilian to obtain functional equivalents. The art provides the sequence of the entire hTERT gene which allows the ordinary artisan to obtain equivalent primers. With regard to structural similarity, the primers of Kilian and the primers of the instant invention are both positioned region suggested by applicant as ideal, namely in the B-deletion, specifically exon 8, and upstream of the B-deletion. Thus, the primers have the same function to amplify the hTERT gene, in the same region, such that the primers would be expected to amplify only nucleic acids which lacked the deletion of exon 7 and 8, the B-deletion. Thus, as discussed above, the primers may be considered structural and functional homologues. The response provides an analysis of the primer of SEQ ID NO: 4 to the full length hTERT sequence. It is noted that the examiner has asserted that given the primers of Kilian, it would have been obvious to have altered those primers in view of the full length. The examiner did not assert that the primer is equivalent to the full length. With respect to the argument in the response that the primer does not even contain the sequence of SEQ ID NO: 4 as a subsequence, but rather contains the reverse complement. This argument has been reviewed but is not convincing because as seen in Kilian, HT2356, is also not found in the mRNA sequence, but is the reverse complement of the sequence such that the sequence may amplify the hTERT gene. It is

obvious to make a primer which is the complement of mRNA for benefit of amplifying the mRNA, as illustrated by Kilian.

The response asserts that the examiner based the rejection on an improper "obvious to try" standard. This argument has been reviewed but is not convincing because the obvious to try standard is applicable when there is no reasonable expectation of success. In this case, the art has provided primers in the same general regions as the instant primers, the full length sequence, thus, altering primer sequences to optimize the results of the primers does not constitute obvious to try. One of ordinary skill in the art would have had a reasonable expectation of success of obtaining equivalent primers to those of Kilian i.e., the sequence for the complete gene was known, desire to select primers in this region is taught by Kilian, parameters which effect primer annealing and specificity of amplification were well known in the art. It is routine experimentation to obtain additional primers having the same functional properties as the primers claimed. The examiner agrees that "obvious to try" is not an appropriate basis for a 103 rejection, but disagrees that the cited references do not provide an expectation for success. That is, one of ordinary skill in the art would have a reasonable expectation for success. Obviousness does not require absolute predictability but only the reasonable expectation of success. See In re Merck and Company Inc., 800 F. 2d 1091, 231 USPQ 375 (Fed. Cir. 1986) and In re O'Farrell, 7 USPQ2d 1673 (Fed. Cir. 1988).

The response asserts that the Examiner improperly ignored the unexpected benefit of the claimed primers that are described in the specification. This argument

has been reviewed but is not convincing because the response has not compared the instant primers to the closest prior art (see MPEP 716.02(e)). The response compares the performance of primers in exon 3 and 4 with the instant primers. The response fails to compare the primer pair of Kilian to the instant primers. As specifically provided in the response, the response has compared the primers of Hisatomi with the instant primers. The response states, "these primers hybridize to regions in exons 3 and 4, respectively, and, therefore, are not capable of selectively amplifying hTERT mRNA containing the B region (exons 7 and 8)" (pg 14 of response filed June 18, 2001). The primers of Kilian however are capable of selectively amplifying hTERT mRNA containing the B-region. The argument provided by the rejection, remains that primers within exon 8, especially those which overlap the instant primer 4, would be functional equivalents such that the would amplify the nucleic acid only when the B-deletion was not deleted. Thus, in order to establish unexpected results, a comparison of the closest prior art is required.

For the convenience and clarity of the issue, the following diagram has been provided to illustrate the positioning of the primers of Kilian and the instant application.

2101 cctggacgatatccacagggcctggcgcaccttcgtgctgcgtgtgcgggcccaggaccc
2161 gccgcctgagctgtacttgtcaaggtggatgtgacgggcgcgtacgacaccatccccca
2221 ggacaggctcacggaggtcatcgccagcatcatcaaaccccagaacacgtactgcgtgcg
2281 tcggtatgccgtggtccagaaggccgcccatgggcacgtccgcaaggccttcaagagcca
2341 cgtctctaccttgacagacctccagccgtacatgcgacagttcgtggctcacctgcagga
2401 gaccagcccgctgagggatgccgtcgtcatcgagcagagctcctccctgaatgaggccag
2461 cagtggcctcttcgacgtcttcctacgcttcatgtgccaccacgccgtgcgcatcagggg
2521 caagtcctacgtccagtgccaggggatcccgcagggctccatcctctccacgctgctctg
2581 cagcctgtgctacggcgacatggagaacaagctgtttgcggggattcggcgggacgggct
2641 gctcctgcgtttggtggatgatttcttgttggtgacacctcacctcacccacgcgaaaac

The primers highlighted are the primers taught in the art, namely Kilian Primer HT2026F and HT2356R. The primers underlined are the primers taught in the instant specification, namely SEQ ID NO: 2, 4 and 5. It is clear that both the specification and the art teach a primer pair which contains one primer within exon 8, within the B-deletion, and the second primer upstream of exon 7, outside of the B-deletion. With respect to the probes of Claim 7, 19-20, it was well known in the art, that identification of amplified products may be performed by probing within the region of the amplified product. Probes 6-8 are located within the amplified region.

Thus for the reasons above and those already of record, the rejection is maintained.

6. Claims 21, 23, 25-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kilian et al (Human Molecular Genetics, Vol. 6, No. 12, pg. 2011-2019, 1997) in view of Hudkins et al. (US Pat. 5,475,110, December 1995) in view of Nakamura et al (Genbank Accession Number AF015950, August 1997) as applied to Claims 1, 3, 5-7, 15-16 above, and further in view of Nakamura (Science, Vol 277, pg 955-959, August 1997).

Neither Kilian nor Hudkins specifically teach a method for identifying the presence of cancerous cells by quantitating the hTERT mRNA.

However, Nakamura teaches that hTRT is expressed in immortal (cancerous) cell strains. As seen in Figure 3, hTRT is not expressed in telomerase-negative mortal cell lines (pg 958, col. 1). Nakamura teaches that telomerase activity was more

strongly correlated with the abundance of hTRT mRNA than with that of telomerase RNA. Additionally, Nakamura teaches that the correlation of its mRNA expression level with activity also supports this conclusion (pg 958, col. 1). Moreover, Nakamura teaches that the correlation between hTRT mRNA levels and human telomerase activity shown here indicates that hTRT has promise for cancer diagnosis (pg 958, col. 3).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of quantitating mRNA as taught by Kilian and Hudkins with the teachings of telomerase activity of Nakamura. The ordinary artisan would have realized based upon the teachings of Nakamura that once the expression level of hTRT was obtained the identification of mortal versus immortal cells could be identified as provided in Figure 3 of Nakamura. Moreover, the explict statement provided by Nakamura which teaches that the correlation between hTRT mRNA levels and human telomerase activity shown here indicates that hTRT has promise for cancer diagnosis (pg 958, col. 3).

Response to Arguments

The response traverses the rejection. The response asserts that the claimed primers are not obvious. The response assert that the particular primers are critical aspect of all of the claims since the particular primers enable a significantly improved quantiation of hTERT mRNA.

The response asserts that the particular primers are not structural and functional homologues of the full length hTERT sequence. This argument has been reviewed but is not convincing because as stated in the rejection above, it would have been prima

facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the primers of Kilan for detection of hTERT mRNA since the entire hTERT sequence was taught and characterized by Nakamura. Given the primers taught in the art, namely HT2026F and HT2356R of Kilian, the ordinary artisan would have been motivated to have modified the primers of Kilian to obtain functional equivalents. The art provides the sequence of the entire hTERT gene which allows the ordinary artisan to obtain equivalent primers. With regard to structural similarity, the primers of Kilian and the primers of the instant invention are both positioned region suggested by applicant as ideal, namely in the B-deletion, specifically exon 8, and upstream of the B-deletion. Thus, the primers have the same function to amplify the hTERT gene, in the same region, such that the primers would be expected to amplify only nucleic acids which lacked the deletion of exon 7 and 8, the B-deletion. Thus, as discussed above, the primers may be considered structural and functional homologues. The response provides an analysis of the primer of SEQ ID NO: 4 to the full length hTERT sequence. It is noted that the examiner has asserted that given the primers of Kilian, it would have been obvious to have altered those primers in view of the full length. The examiner did not assert that the primer is equivalent to the full length. With respect to the argument in the response that the primer does not even contain the sequence of SEQ ID NO: 4 as a subsequence, but rather contains the reverse complement. This argument has been reviewed but is not convincing because as seen in Kilian, HT2356, is also not found in the mRNA sequence, but is the reverse complement of the sequence such that the sequence may amplify the hTERT gene. It is

obvious to make a primer which is the complement of mRNA for benefit of amplifying the mRNA, as illustrated by Kilian.

The response asserts that the examiner based the rejection on an improper "obvious to try" standard. This argument has been reviewed but is not convincing because the obvious to try standard is applicable when there is no reasonable expectation of success. In this case, the art has provided primers in the same general regions as the instant primers, the full length sequence, thus, altering primer sequences to optimize the results of the primers does not constitute obvious to try. One of ordinary skill in the art would have had a reasonable expectation of success of obtaining equivalent primers to those of Kilian i.e., the sequence for the complete gene was known, desire to select primers in this region is taught by Kilian, parameters which effect primer annealing and specificity of amplification were well known in the art. It is routine experimentation to obtain additional primers having the same functional properties as the primers claimed. The examiner agrees that "obvious to try" is not an appropriate basis for a 103 rejection, but disagrees that the cited references do not provide an expectation for success. That is, one of ordinary skill in the art would have a reasonable expectation for success. Obviousness does not require absolute predictability but only the reasonable expectation of success. See In re Merck and Company Inc., 800 F. 2d 1091, 231 USPQ 375 (Fed. Cir. 1986) and In re O'Farrell, 7 USPQ2d 1673 (Fed. Cir. 1988).

The response asserts that the Examiner improperly ignored the unexpected benefit of the claimed primers that are described in the specification. This argument

has been reviewed but is not convincing because the response has not compared the instant primers to the closest prior art (see MPEP 716.02(e)). The response compares the performance of primers in exon 3 and 4 with the instant primers. The response fails to compare the primer pair of Kilian to the instant primers. As specifically provided in the response, the response has compared the primers of Hisatomi with the instant primers. The response states, "these primers hybridize to regions in exons 3 and 4, respectively, and, therefore, are not capable of selectively amplifying hTERT mRNA containing the B region (exons 7 and 8)" (pg 14 of response filed June 18, 2001). The primers of Kilian however are capable of selectively amplifying hTERT mRNA containing the B-region. The argument provided by the rejection, remains that primers within exon 8, especially those which overlap the instant primer 4, would be functional equivalents such that the would amplify the nucleic acid only when the B-deletion was not deleted. Thus, in order to establish unexpected results, a comparison of the closest prior art is required.

For the convenience and clarity of the issue, the following diagram has been provided to illustrate the positioning of the primers of Kilian and the instant application.

2101 cctggacgatatccacagggcctggcgcaccttcgtgctgcgtgtgcgggcccaggaccc
2161 gccgcctgagctgtacttgtcaaggtggatgtgacgggcgcgtacgacaccatccccca
2221 ggacaggctcacggaggtcatcgccagcatcatcaaaccccagaacacgtactgcgtgcg
2281 tcggtatgccgtggtccagaaggccgcccatgggcacgtccgcaaggccttcaagagcca
2341 cgtctctaccttgacagacctccagccgtacatgcgacagttcgtggctcacctgcagga
2401 gaccagcccgctgagggatgccgtcgtcatcgagcagagctcctccctgaatgaggccag
2461 cagtggcctcttcgacgtcttcctacgcttcatgtgccaccacgccgtgcgcatcagggg
2521 caagtcctacgtccagtgccaggggatcccgcagggctccatcctctccacgctgctctg
2581 cagcctgtgctacggcgacatggagaacaagctgtttgcggggattcggcgggacgggct
2641 gctcctgcgtttggtggatgatttcttgttggtgacacctcacctcacccacgcgaaaac

The primers highlighted are the primers taught in the art, namely Kilian Primer HT2026F and HT2356R. The primers underlined are the primers taught in the instant specification, namely SEQ ID NO: 2, 4 and 5. It is clear that both the specification and the art teach a primer pair which contains one primer within exon 8, within the B-deletion, and the second primer upstream of exon 7, outside of the B-deletion. With respect to the probes of Claim 7, 19-20, it was well known in the art, that identification of amplified products may be performed by probing within the region of the amplified product. Probes 6-8 are located within the amplified region.

Thus for the reasons above and those already of record, the rejection is maintained.

7. Claims 1, 3, 5-8, 10, 12-14, 21, 23, 25-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kilian et al (Human Molecular Genetics, Vol. 6, No. 12, pg. 2011-2019, 1997) in view of Hisatomi et al. (International J. of Oncology, Vol 14, pg 727-732, 1999) further in view of Nakamura et al (Genbank Accession Number AF015950, August 1997).

Kilian et al. (herein referred to as Kilian) teaches the beta deletion in the hTCS1 gene (also referred to as hTERT, see specification pg. 1). Kilian teaches that the beta-exon deletion encode truncated proteins. Kilian teaches regions surrounding the beta-exon deletion region (see Figure 5). Kilian teaches numerous oligonucleotide primers which include HT2356R. HT2356R is located within exon 8 and overlaps the last 7 nucleotides of SEQ ID NO: 4. Kilian teaches that hTCS1 is differentially expressed in normal and tumor tissues. As seen in Figure 4, TR-PCR was carried out on RNA with

primer combinations including HT2356R. Kilian teaches southern and Northern analysis using P-labeled probes, RT-PCR analysis using electrophoresis in a agarose gel and probing with a radiolabeled oligonucleotide (pg 2017, col. 2). Finally, Kilian teaches that the beta-exon deletion encodes a truncated protein.

While Kilian teaches probing with radiolabeled probes and studying of expression levels, it is not apparent that Kilian explicitly teaches quantifying the PCR product obtained. Kilian also does not teach identifying the presence of cancerous cells by hTERT quantitiy.

However, Hisatomi et al. (herein referred to as Hisatomi) teaches that levels of hTERT mRNA was investigated with regard to tumor tissue and non-cancerous tissues. The difference of hTERT mRNA level was highly significant between the tumor tissue and the non-cancerous liver tissue (abstract). Moreover, a strong correlation between the levels of hTERT mRNA and that of telomerase activity in HCC was observed (abstract). HTERT mRNA was amplifies using primers, a real-time PCR system provided the essential information to quantify the initial target copy number (pg 728, col. 1). The levels of hTERT mRNA were provided (pg 728, col. 2) and significance was shown. As seen in Figure 2, quantification of hTERT mRNA was plotted relative to the tumor or nontumor status of the tissue (limitations of Claim 1, 21). A cutoff was provided at 1.16 such that hTERT above this "threshold" were at risk for being cancerous. As seen in Figure 4, a correlation between the quantification of hTERT mRNA and telomerase activity is provided such that telomerase activity may be assessed from the mRNA of hTERT (limitations of Claim 8).

While Kilian teaches a primer which is located in exon 8 and overlaps the last 7 nucleotides of SEQ ID NO: 4, neither Hisatomi nor Kilian specifically teach the primers and probes of the instant case.

Nakamura however teaches the entire sequence of the hTERT gene.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the primers of Kilan for detection of hTERT mRNA since the entire hTERT sequence was taught and characterized by Nakamura. Additionally, in the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologues, *however*, the court stated

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologues because homologues often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed primers simply represent structural and functional homologues of the full length disclosed hTERT sequence concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited reference in the absence of secondary considerations. Designing primers and probes which are equivalents to those taught in the art is routine experimentation. The ordinary artisan would have been motivated to have designed probes and primers based upon the sequence of Nakurma

which were equivalents to those provided by Kilian. Absent factual evidence that the instant primers have unexpected benefits or properties such that they would not be equivalents to those provided in the art, the claimed primers are merely functional equivalents of the primers provided in the art for amplifying the hTERT gene.

Moreover, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kilian which detects mRNA of hTCS1 with the method of Hisatomi which quantifies the RNA expression level in log copies/ug total RNA. The skilled artisan would have been motivated to have quantitated the mRNA obtained in the method of Kilian for the expected benefit of quantifying the amount of mRNA present for utilization in expression level comparison as taught by Hisatomi. The skilled artisan would have been motivated to have quantitated the results from Kilian for analysis as provided by Hisatomi. Hisatomi teaches using the expression levels for comparing expression in cancerous versus normal cells such that data may be obtained for diagnostics such that if hTERT level is greater than the "threshold" the cells were considered cancerous.

Response to Arguments

The response traverses the rejection. The response asserts that the claimed primers are not obvious. The response assert that the particular primers are critical aspect of all of the claims since the particular primers enable a significantly improved quantiation of hTERT mRNA.

The response asserts that the particular primers are not structural and functional homologues of the full length hTERT sequence. This argument has been reviewed but

is not convincing because as stated in the rejection above, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the primers of Kilan for detection of hTERT mRNA since the entire hTERT sequence was taught and characterized by Nakamura. Given the primers taught in the art, namely HT2026F and HT2356R of Kilian, the ordinary artisan would have been motivated to have modified the primers of Kilian to obtain functional equivalents. The art provides the sequence of the entire hTERT gene which allows the ordinary artisan to obtain equivalent primers. With regard to structural similarity, the primers of Kilian and the primers of the instant invention are both positioned region suggested by applicant as ideal, namely in the B-deletion, specifically exon 8, and upstream of the B-deletion. Thus, the primers have the same function to amplify the hTERT gene, in the same region, such that the primers would be expected to amplify only nucleic acids which lacked the deletion of exon 7 and 8, the B-deletion. Thus, as discussed above, the primers may be considered structural and functional homologues. The response provides an analysis of the primer of SEQ ID NO: 4 to the full length hTERT sequence. It is noted that the examiner has asserted that given the primers of Kilian, it would have been obvious to have altered those primers in view of the full length. The examiner did not assert that the primer is equivalent to the full length. With respect to the argument in the response that the primer does not even contain the sequence of SEQ ID NO: 4 as a subsequence, but rather contains the reverse complement. This argument has been reviewed but is not convincing because as seen in Kilian, HT2356, is also not found in the mRNA sequence, but is the reverse

complement of the sequence such that the sequence may amplify the hTERT gene. It is obvious to make a primer which is the complement of mRNA for benefit of amplifying the mRNA, as illustrated by Kilian.

The response asserts that the examiner based the rejection on an improper "obvious to try" standard. This argument has been reviewed but is not convincing because the obvious to try standard is applicable when there is no reasonable expectation of success. In this case, the art has provided primers in the same general regions as the instant primers, the full length sequence, thus, altering primer sequences to optimize the results of the primers does not constitute obvious to try. One of ordinary skill in the art would have had a reasonable expectation of success of obtaining equivalent primers to those of Kilian i.e., the sequence for the complete gene was known, desire to select primers in this region is taught by Kilian, parameters which effect primer annealing and specificity of amplification were well known in the art. It is routine experimentation to obtain additional primers having the same functional properties as the primers claimed. The examiner agrees that "obvious to try" is not an appropriate basis for a 103 rejection, but disagrees that the cited references do not provide an expectation for success. That is, one of ordinary skill in the art would have a reasonable expectation for success. Obviousness does not require absolute predictability but only the reasonable expectation of success. See In re Merck and Company Inc., 800 F. 2d 1091, 231 USPQ 375 (Fed. Cir. 1986) and In re O'Farrell, 7 USPQ2d 1673 (Fed. Cir. 1988).

The response asserts that the Examiner improperly ignored the unexpected benefit of the claimed primers that are described in the specification. This argument has been reviewed but is not convincing because the response has not compared the instant primers to the closest prior art (see MPEP 716.02(e)). The response compares the performance of primers in exon 3 and 4 with the instant primers. The response fails to compare the primer pair of Kilian to the instant primers. As specifically provided in the response, the response has compared the primers of Hisatomi with the instant primers. The response states, "these primers hybridize to regions in exons 3 and 4, respectively, and, therefore, are not capable of selectively amplifying hTERT mRNA containing the B region (exons 7 and 8)" (pg 14 of response filed June 18, 2001). The primers of Kilian however are capable of selectively amplifying hTERT mRNA containing the B-region. The argument provided by the rejection, remains that primers within exon 8, especially those which overlap the instant primer 4, would be functional equivalents such that the would amplify the nucleic acid only when the B-deletion was not deleted. Thus, in order to establish unexpected results, a comparison of the closest prior art is required.

For the convenience and clarity of the issue, the following diagram has been provided to illustrate the positioning of the primers of Kilian and the instant application.

2101 cctggacgatatccacagggcctggcgcaccttcgtgctgcgtgtgcgggcccaggaccc
2161 gccgcctgagctgtacttttgtcaaggtggatgtgacgggcgcgtacgacaccatccccca
2221 ggacaggctcacggaggtcatcgccagcatcatcaaaccccagaacacgtactgcgtgcg
2281 tcggtatgccgtggtccagaaggccgcccatgggcacgtccgcaaggccttcaagagcca
2341 cgtctctaccttgacagacctccagccgtacatgcgacagttcgtggctcacctgcagga
2401 gaccagcccgctgagggatgccgtcgtcatcgagcagagctcctccctgaatgaggccag
2461 cagtggcctcttcgacgtcttcctacgcttcatgtgccaccacgccgtgcgcatcagggg
2521 caagtcctacgtccagtgccaggggatcccgcagggctccatcctctccacgctgctctg
2581 cagcctgtgctacggcgacatggagaacaagctgtttgcggggattcggcgggacgggct

2641 gctcctgcgtttggtggatgatttcttgttggtgacacctcacctcacccacgcgaaaac

The primers highlighted are the primers taught in the art, namely Kilian Primer HT2026F and HT2356R. The primers underlined are the primers taught in the instant specification, namely SEQ ID NO: 2, 4 and 5. It is clear that both the specification and the art teach a primer pair which contains one primer within exon 8, within the B-deletion, and the second primer upstream of exon 7, outside of the B-deletion. With respect to the probes of Claim 7, 19-20, it was well known in the art, that identification of amplified products may be performed by probing within the region of the amplified product. Probes 6-8 are located within the amplified region.

Thus for the reasons above and those already of record, the rejection is maintained.

8. Claims 1, 3, 5-7, 21, 23, 25-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kilian et al (Human Molecular Genetics, Vol. 6, No. 12, pg. 2011-2019, 1997) in view of Meyerson et al. (Cell, Vol 90, pg 785-795, August 1997) further in view of Nakamura et al (Genbank Accession Number AF015950, August 1997).

Kilian et al. (herein referred to as Kilian) teaches the beta deletion in the hTCS1 gene (also referred to as hTERT, see specification pg. 1). Kilian teaches that the beta-exon deletion encode truncated proteins. Kilian teaches regions surrounding the beta-exon deletion region (see Figure 5). Kilian teaches numerous oligonucleotide primers which include HT2356R. HT2356R is located within exon 8 and overlaps the last 7 nucleotides of SEQ ID NO: 4. Kilian teaches that hTCS1 is differentially expressed in normal and tumor tissues. As seen in Figure 4, TR-PCR was carried out on RNA with

primer combinations including HT2356R. Kilian teaches southern and Northern analysis using P-labeled probes, RT-PCR analysis using electrophoresis in a agarose gel and probing with a radiolabeled oligonucleotide (pg 2017, col. 2). Finally, Kilian teaches that the beta-exon deletion encodes a truncated protein.

While Kilian teaches probing with radiolabeled probes and studying of expression levels, it is not apparent that Kilian explicitly teaches quantifying the PCR product obtained. Kilian also does not teach identifying the presence of cancerous cells by hTERT quantitiy.

However, Meyerson teaches hEST2 (hTERT) is expressed at high levels in primary tumors, cancer cell lines, and telomerase-positive tissues, but is undetectalbe in telomerase negative cell lines (abstract). Meyerson teaches that activation of telomerase also appears to be a major step in the progression of human cancers (pg 786, col. 1). Meyerson teaches that "we analzyed the expression levels of hEST2 mRNA in various cell types, using both RNA Northern hybridizations and Rnase protection assays to do so" (pg 789, col. 2). Thus, Meyerson necessarily has quantitated the mRNA of hEST2 since an expression level was obtained. Moreover as seen in Figure 4, hEST2 mRNA was strongly expressed in a variety of cancer cell lines (pg 790, col. 1).

While Kilian teaches a primer which is located in exon 8 and overlaps the last 7 nucleotides of SEQ ID NO: 4, neither Myerson nor Kilian specifically teach the primers and probes of the instant case.

Nakamura however teaches the entire sequence of the hTERT gene.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the primers of Kilan for detection of hTERT mRNA since the entire hTERT sequence was taught and characterized by Nakamura. Addtionally, in the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologues, *however*, the court stated

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologues because homologues often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed primers simply represent structural and functional homologues of the full length disclosed hTERT sequence concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited reference in the absence of secondary considerations. Designing primers and probes which are equivalents to those taught in the art is routine experimentation. The ordinary artisan would have been motivated to have designed probes and primers based upon the sequence of Nakurma which were equivalents to those provided by Kilian. Absent factual evidence that the instant primers have unexpected benefits or properties such that they would not be equivalents to those provided in the art, the claimed primers are merely functional equivalents of the primers provided in the art for amplifying the hTERT gene.

Moreover, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kilian which detects mRNA of hTCS1 with the method of Meyerson which quantifies the RNA expression level. The skilled artisan would have been motivated to have quantitated the mRNA obtained in the method of Kilian for the expected benefit of quantifying the amount of mRNA present for utilization in expression level comparison as taught by Meyerson. The skilled artisan would have been motivated to have quantitated the results from Kilian for analysis as provided by Meyerson. Meyerson teaches using the expression levels for comparing expression in cancerous versus normal cells such that data may be obtained for diagnostics.

Response to Arguments

The response traverses the rejection. The response asserts that the claimed primers are not obvious. The response assert that the particular primers are critical aspect of all of the claims since the particular primers enable a significantly improved quantiation of hTERT mRNA.

The response asserts that the particular primers are not structural and functional homologues of the full length hTERT sequence. This argument has been reviewed but is not convincing because as stated in the rejection above, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the primers of Kilan for detection of hTERT mRNA since the entire hTERT sequence was taught and characterized by Nakamura. Given the primers taught in the art, namely HT2026F and HT2356R of Kilian, the ordinary artisan would

have been motivated to have modified the primers of Kilian to obtain functional equivalents. The art provides the sequence of the entire hTERT gene which allows the ordinary artisan to obtain equivalent primers. With regard to structural similarity, the primers of Kilian and the primers of the instant invention are both positioned region suggested by applicant as ideal, namely in the B-deletion, specifically exon 8, and upstream of the B-deletion. Thus, the primers have the same function to amplify the hTERT gene, in the same region, such that the primers would be expected to amplify only nucleic acids which lacked the deletion of exon 7 and 8, the B-deletion. Thus, as discussed above, the primers may be considered structural and functional homologues. The response provides an analysis of the primer of SEQ ID NO: 4 to the full length hTERT sequence. It is noted that the examiner has asserted that given the primers of Kilian, it would have been obvious to have altered those primers in view of the full length. The examiner did not assert that the primer is equivalent to the full length. With respect to the argument in the response that the primer does not even contain the sequence of SEQ ID NO: 4 as a subsequence, but rather contains the reverse complement. This argument has been reviewed but is not convincing because as seen in Kilian, HT2356, is also not found in the mRNA sequence, but is the reverse complement of the sequence such that the sequence may amplify the hTERT gene. It is obvious to make a primer which is the complement of mRNA for benefit of amplifying the mRNA, as illustrated by Kilian.

The response asserts that the examiner based the rejection on an improper "obvious to try" standard. This argument has been reviewed but is not convincing

because the obvious to try standard is applicable when there is no reasonable expectation of success. In this case, the art has provided primers in the same general regions as the instant primers, the full length sequence, thus, altering primer sequences to optimize the results of the primers does not constitute obvious to try. One of ordinary skill in the art would have had a reasonable expectation of success of obtaining equivalent primers to those of Kilian i.e., the sequence for the complete gene was known, desire to select primers in this region is taught by Kilian, parameters which effect primer annealing and specificity of amplification were well known in the art. It is routine experimentation to obtain additional primers having the same functional properties as the primers claimed. The examiner agrees that "obvious to try" is not an appropriate basis for a 103 rejection, but disagrees that the cited references do not provide an expectation for success. That is, one of ordinary skill in the art would have a reasonable expectation for success. Obviousness does not require absolute predictability but only the reasonable expectation of success. See In re Merck and Company Inc., 800 F. 2d 1091, 231 USPQ 375 (Fed. Cir. 1986) and In re O'Farrell, 7 USPQ2d 1673 (Fed. Cir. 1988).

The response asserts that the Examiner improperly ignored the unexpected benefit of the claimed primers that are described in the specification. This argument has been reviewed but is not convincing because the response has not compared the instant primers to the closest prior art (see MPEP 716.02(e)). The response compares the performance of primers in exon 3 and 4 with the instant primers. The response fails to compare the primer pair of Kilian to the instant primers. As specifically provided in the

response, the response has compared the primers of Hisatomi with the instant primers. The response states, "these primers hybridize to regions in exons 3 and 4, respectively, and, therefore, are not capable of selectively amplifying hTERT mRNA containing the B region (exons 7 and 8)" (pg 14 of response filed June 18, 2001). The primers of Kilian however are capable of selectively amplifying hTERT mRNA containing the B-region. The argument provided by the rejection, remains that primers within exon 8, especially those which overlap the instant primer 4, would be functional equivalents such that the would amplify the nucleic acid only when the B-deletion was not deleted. Thus, in order to establish unexpected results, a comparison of the closest prior art is required.

For the convenience and clarity of the issue, the following diagram has been provided to illustrate the positioning of the primers of Kilian and the instant application.

2101 cctggacgatatccacagggcctggcgcaccttcgtgctgcgtgtgcgggcccaggaccc
2161 gccgcctgagctgtacttgtcaaggtggatgtgacgggcgcgtacgacaccatccccca
2221 ggacaggctcacggaggtcatcgccagcatcatcaaaccccagaacacgtactgcgtgcg
2281 tcggtatgccgtggtccagaaggccgcccatgggcacgtccgcaaggccttcaagagcca
2341 cgtctctaccttgacagacctccagccgtacatgcgacagttcgtggctcacctgcagga
2401 gaccagcccgctgagggatgccgtcgtcatcgagcagagctcctccctgaatgaggccag
2461 cagtggcctcttcgacgtcttcctacgcttcatgtgccaccacgccgtgcgcatcagggg
2521 caagtcctacgtccagtgccaggggatcccgcagggctccatcctctccacgctgctctg
2581 cagcctgtgctacggcgacatggagaacaagctgtttgcggggattcggcgggacgggct
2641 gctcctgcgtttggtggatgatttcttgttggtgacacctcacctcacccacgcgaaaac

The primers highlighted are the primers taught in the art, namely Kilian Primer HT2026F and HT2356R. The primers underlined are the primers taught in the instant specification, namely SEQ ID NO: 2, 4 and 5. It is clear that both the specification and the art teach a primer pair which contains one primer within exon 8, within the B-deletion, and the second primer upstream of exon 7, outside of the B-deletion. With

respect to the probes of Claim 7, 19-20, it was well known in the art, that identification of amplified products may be performed by probing within the region of the amplified product. Probes 6-8 are located within the amplified region.

Thus for the reasons above and those already of record, the rejection is maintained.

9. Claims 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kilian et al (Human Molecular Genetics, Vol. 6, No. 12, pg. 2011-2019, 1997) in view of Hudkins et al. (US Pat. 5,475,110, December 1995) as applied to Claims 1, 3, 5-7, 15-16 above, in view of Nakamura et al (Genbank Accession Number AF015950, August 1997) in further view of Stratagene Catalog (1988).

Neither Kilian, nor Nakamura specifically teach placing the primers in a kit.

However, Stratagene teaches gene characterization kits.

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the oligonucleotides of Kilian and Nakamura to place the necessary reagents in kit, as taught by Stratagene, for the expected benefit of convenience and quality control. The ordinary artisan would be motivated to have packaged the primers into a kit to reduce waste, save money, increase quality control and save time, as taught by Stratagene.

Response to Arguments

The response traverses the rejection. The response asserts that the claimed primers are not obvious. The response assert that the particular primers are critical

aspect of all of the claims since the particular primers enable a significantly improved quantiation of hTERT mRNA.

The response asserts that the particular primers are not structural and functional homologues of the full length hTERT sequence. This argument has been reviewed but is not convincing because as stated in the rejection above, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the primers of Kilan for detection of hTERT mRNA since the entire hTERT sequence was taught and characterized by Nakamura. Given the primers taught in the art, namely HT2026F and HT2356R of Kilian, the ordinary artisan would have been motivated to have modified the primers of Kilian to obtain functional equivalents. The art provides the sequence of the entire hTERT gene which allows the ordinary artisan to obtain equivalent primers. With regard to structural similarity, the primers of Kilian and the primers of the instant invention are both positioned region suggested by applicant as ideal, namely in the B-deletion, specifically exon 8, and upstream of the B-deletion. Thus, the primers have the same function to amplify the hTERT gene, in the same region, such that the primers would be expected to amplify only nucleic acids which lacked the deletion of exon 7 and 8, the B-deletion. Thus, as discussed above, the primers may be considered structural and functional homologues. The response provides an analysis of the primer of SEQ ID NO: 4 to the full length hTERT sequence. It is noted that the examiner has asserted that given the primers of Kilian, it would have been obvious to have altered those primers in view of the full length. The examiner did not assert that the primer is equivalent to the full length. With

respect to the argument in the response that the primer does not even contain the sequence of SEQ ID NO: 4 as a subsequence, but rather contains the reverse complement. This argument has been reviewed but is not convincing because as seen in Kilian, HT2356, is also not found in the mRNA sequence, but is the reverse complement of the sequence such that the sequence may amplify the hTERT gene. It is obvious to make a primer which is the complement of mRNA for benefit of amplifying the mRNA, as illustrated by Kilian.

The response asserts that the examiner based the rejection on an improper "obvious to try" standard. This argument has been reviewed but is not convincing because the obvious to try standard is applicable when there is no reasonable expectation of success. In this case, the art has provided primers in the same general regions as the instant primers, the full length sequence, thus, altering primer sequences to optimize the results of the primers does not constitute obvious to try. One of ordinary skill in the art would have had a reasonable expectation of success of obtaining equivalent primers to those of Kilian i.e., the sequence for the complete gene was known, desire to select primers in this region is taught by Kilian, parameters which effect primer annealing and specificity of amplification were well known in the art. It is routine experimentation to obtain additional primers having the same functional properties as the primers claimed. The examiner agrees that "obvious to try" is not an appropriate basis for a 103 rejection, but disagrees that the cited references do not provide an expectation for success. That is, one of ordinary skill in the art would have a reasonable expectation for success. Obviousness does not require absolute

predictability but only the reasonable expectation of success. See In re Merck and Company Inc., 800 F. 2d 1091, 231 USPQ 375 (Fed. Cir. 1986) and In re O'Farrell, 7 USPQ2d 1673 (Fed. Cir. 1988).

The response asserts that the Examiner improperly ignored the unexpected benefit of the claimed primers that are described in the specification. This argument has been reviewed but is not convincing because the response has not compared the instant primers to the closest prior art (see MPEP 716.02(e)). The response compares the performance of primers in exon 3 and 4 with the instant primers. The response fails to compare the primer pair of Kilian to the instant primers. As specifically provided in the response, the response has compared the primers of Hisatomi with the instant primers. The response states, "these primers hybridize to regions in exons 3 and 4, respectively, and, therefore, are not capable of selectively amplifying hTERT mRNA containing the B region (exons 7 and 8)" (pg 14 of response filed June 18, 2001). The primers of Kilian however are capable of selectively amplifying hTERT mRNA containing the B-region. The argument provided by the rejection, remains that primers within exon 8, especially those which overlap the instant primer 4, would be functional equivalents such that the would amplify the nucleic acid only when the B-deletion was not deleted. Thus, in order to establish unexpected results, a comparison of the closest prior art is required.

For the convenience and clarity of the issue, the following diagram has been provided to illustrate the positioning of the primers of Kilian and the instant application.

2101 cctggacgatatccacagggcctggcgcaccttcgtgctgcgtgtgcgggcccaggaccc
2161 gccgcctgagctgtactttgtcaaggtggatgtgacgggcgcgtacgacaccatccccca
2221 ggacaggctcacggaggtcatcgccagcatcatcaaaccccagaacacgtactgcgtgcg

2281 tcggtatgccgtggtccagaaggccgcccatgggcacgtccgcaaggccttcaagagcca
2341 cgtctctaccttgacagacctccagccgtacatgcgacagttcgtggctcacctgcagga
2401 gaccagcccgctgagggatgccgtcgtcatcgagcagagctcctccctgaatgaggccag
2461 cagtggcctcttcgacgtcttcctacgcttcatgtgccaccacgccgtgcgcatcagggg
2521 caagtcctacgtccagtgccaggggatcccgcagggctccatcctctccacgctgctctg
2581 cagcctgtgctacggcgacatggagaacaagctgtttgcggggattcggcgggacgggct
2641 gctcctgcgtttggtggatgatttcttgttggtgacacctcacctcacccacgcgaaaac

The primers highlighted are the primers taught in the art, namely Kilian Primer HT2026F and HT2356R. The primers underlined are the primers taught in the instant specification, namely SEQ ID NO: 2, 4 and 5. It is clear that both the specification and the art teach a primer pair which contains one primer within exon 8, within the B-deletion, and the second primer upstream of exon 7, outside of the B-deletion. With respect to the probes of Claim 7, 19-20, it was well known in the art, that identification of amplified products may be performed by probing within the region of the amplified product. Probes 6-8 are located within the amplified region.

Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

10. No claims allowable.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

A) Nakamura-2 teaches that telomerase activity was examined quantitatively in gartrointestinal tissues by using the hybridization protection assay combined with the telomeric repeat amplification protocol (TRAP) to assess the diagnostic utility of measuring telomerase activity to determine the relationship between telomerase activity and human telomerase reverse transcriptase (hTERT expression) (abstract). Nakamura teaches that "the different in hTERT expression levels between cancerous and noncancerous tissues was less the mean expression level was higher in cancerous tissues than in noncancerous tissues" (pg 317, col. 1). Thus, Nakamura necessarily has quantified the hTERT levels. Moreover, using the hTERT expression levels and the plots of Figure 4, the telomerase activity may be quantitated. Finally, as provided in Figure 4, cancerous cells may be identified by their hTERT activity. Nakamura also teaches that more than "twice higher hTERT expression in tumor than in non-tumor samples from the same patient was observed (pg 319-320).

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Enewold Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Thursday from 7:00AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Enewold Goldberg
July 19, 2001

Lisa B. Arthur

LISA B. ARTHUR
PRIMARY EXAMINER
GROUP ~~1800~~ 1600